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***Guidance on
the use of
routine antenatal
anti-D prophylaxis
for RhD-negative
women***

Technology Appraisal No. 41

Guidance on the use of routine antenatal anti-D prophylaxis for RhD-negative women

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This guidance is written in the following context:

This guidance represents the view of the Institute, which was arrived at after careful consideration of the available evidence. Health professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

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Guidance on the use of routine antenatal anti-D prophylaxis for RhD-negative women

1. Guidance

- 1.1 It is recommended that routine antenatal anti-D prophylaxis (RAADP) is offered to all non-sensitised pregnant women who are RhD negative.
- 1.2 The clinician (obstetrician, midwife or general practitioner) responsible for the prenatal care of a non-sensitised RhD-negative woman should discuss with her RAADP and the options available so that the woman can make an informed choice about treatment. This discussion should include the circumstances where RAADP would be neither necessary nor cost effective. Such circumstances might include those where the woman:
 - has opted to be sterilised after the birth of the baby
 - is in a stable relationship with the father of the child, and the father is known or found to be RhD-negative
 - is certain that she will not have another child after her current pregnancy.

The difference between RAADP (i.e. routine prophylaxis at 28 and 34 weeks) and prophylactic anti-D given because of likely sensitisation (see 1.3 below) should be clearly explained to the woman.

- 1.3 A woman's use of RAADP at 28 and 34 weeks should not be affected by whether she has already had antenatal anti-D prophylaxis (AADP) for a potentially sensitising event early in pregnancy. A woman's use of postpartum anti-D prophylaxis should similarly not be affected by whether she has had RAADP or AADP as the result of a sensitising event. Beyond this, AADP for a potentially sensitising event and postpartum anti-D prophylaxis are not the remit of this guidance. These matters are covered by the Royal College of Obstetricians and Gynaecologists' 'Green Top' 1999 guideline: Use of Anti-D Immunoglobulin for Rh Prophylaxis.
- 1.4 It is recommended that high-quality information, validated and produced at the national level, is made available to RhD-negative women and the relevant healthcare professionals.

This section (Section 1) constitutes the Institute's guidance on the use of routine antenatal anti-D prophylaxis for RhD-negative women. The remainder of the document is structured in the following way:

2 Clinical need and practice	Appendix A: Appraisal Committee members
3 The technology	Appendix B: Sources of evidence
4 Evidence	Appendix C: Patient information
5 Implications for the NHS	Appendix D: Technical detail on the criteria for audit of the use of routine antenatal anti-D prophylaxis for RhD-negative women
6 Further research	
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A bi-lingual summary is available from our website at www.nice.org.uk or by telephoning 0870 1555 455 and quoting the reference number N0092.

Mae crynodeb ar gael yn Gymraeg ac yn Saesneg ar ein gwefan yn www.nice.org.uk neu drwy ffonio 0870 1555 455 gan ddyfynnu cyfeirnod N0092.

- 2.1 RhD-negative women who carry an RhD-positive fetus may produce antibodies to the fetal RhD antigens after a fetomaternal haemorrhage (FMH). These antibodies may then cross the placenta in future pregnancies and cause haemolytic disease if the fetus is RhD positive. A woman can also be sensitised by a previous miscarriage, spontaneous or elective abortion, or amniocentesis or other invasive procedure.
- 2.2. Each year in England and Wales there are about 105,000 births to RhD-negative women, some 17% of all births. Of these babies, about 59%, or 62,000, are RhD positive. This represents about 10% of all births each year in England and Wales.
- 2.3. Haemolytic disease of the newborn (HDN) can range in severity from being detectable only in laboratory tests, through to stillbirth, birth of infants with severe disabilities or death of newborn children from anaemia and jaundice. Before immunoprophylaxis became available, the frequency of HDN was 1% of all births and HDN was responsible for the death of one baby in every 2200 births. Anti-D prophylaxis (mostly administered postnatally) and advances in neonatal care have reduced the frequency of HDN by almost a factor of 10, to 1 in 21,000 births. In England and Wales, about 500 fetuses develop haemolytic disease each year, and must be closely monitored. Nevertheless, each year about 25–30 babies die from HDN. In addition, it is believed that fetal loss due to haemolytic disease before 28 weeks' gestation accounts for about 20 spontaneous abortions each year. About 15 children each year will have major permanent developmental problems as a result of HDN, and a further 30 will have minor developmental problems.
- 2.4. In England and Wales, about 30% of hospitals currently offer RAADP to women who are RhD negative. Anti-D prophylaxis is of no use to women who have already been sensitised to the D antigen. No first child of an RhD-negative woman will be affected, unless the mother has been sensitised as a result of a prior miscarriage or abortion or, rarely, by a sensitising event earlier in the pregnancy.
- 2.5. Generally, only subsequent children can be affected when a woman becomes sensitised to RhD antigens. Therefore, RAADP is not necessary for an RhD-negative woman who will be sterilised shortly after the birth and will use effective contraception in the interim period. It may also be unnecessary for a woman who, although not sterilised, is certain that she will have no more children or that the father of her previous children is RhD negative. However, some women subsequently change their minds about whether to have more children, and the RhD status, or the identity, of the father may not be known.

- 3.1 The hyperimmune plasma from which anti-D is produced originates from regular donors and is collected from a number of sites across the USA, all of which comply with US Food and Drug Administration standards. The production process includes steps to minimise the risk of viral contamination. One of the manufacturers, BPL, estimates the chance of contamination with a known virus to be in the order of 1 in 10,000 billion doses. The probability of prion infection is low, as long as the USA remains free of variant Creutzfeldt-Jakob disease (vCJD). In any case, it is not known whether prions can be transmitted between humans via transfused immunoglobulin. For further considerations relating to safety and the related issues of consent and ethics, please see Section 4.3.
- 3.2 At its introduction in the UK in 1969, the recommended standard dose of anti-D was 500 IU. This dose was sufficient to cover more than 99% of FMHs. If a larger haemorrhage was discovered by testing, the woman was given supplementary anti-D. This practice is still reflected in the Royal College of Obstetricians and Gynaecologists' guideline, which recommends a dose of anti-D of at least 500 IU post-delivery and at 28 and 34 weeks' gestation. However, this differs from the standard doses used in some other countries, where 1250–1500 IU is given to all women requiring antenatal or postnatal anti-D prophylaxis; this approach makes testing for larger episodes of FMH less necessary. If the woman has had, or is believed to have had, a sensitising event early in her pregnancy, AADP can be offered earlier, the dose depending on the gestation period. A woman's use of RAADP at 28 and 34 weeks should not be affected by whether she has already had AADP for a potentially sensitising event early in pregnancy.
- 3.3 There are two manufacturers of anti-D immunoglobulin products: BPL and Baxter. For routine antenatal prophylaxis, the licensed dose of anti-D immunoglobulin produced by BPL is at least 500 IU given intramuscularly at 28 and 34 weeks' gestation. The NHS list price of a 500 IU vial is £27.00. Baxter anti-D immunoglobulin BP Immuno is licensed for the prevention of RhD sensitisation; the licensed dose for routine antenatal prophylaxis is 1250 IU given intramuscularly at 28 and 34 weeks' gestation. The NHS list price of the pre-filled syringe for each intramuscular injection is £23.90. (Actual prices for both BPL and Baxter products are subject to contract negotiations.)
- 3.4 Occasionally anti-D prophylaxis causes allergic responses in the mother, but these are rare.

4.1 Clinical effectiveness

4.1.1 Meta-analysis was conducted on three groups of studies:

- Group 1, involving 6400 women, included the results of four studies (one randomised, three non-randomised) which used a regimen of 500 IU at 28 weeks and 34 weeks and reported results for primigravidae. The rate of postnatal anti-D sensitisation was 0.89% (95% confidence interval (CI) 0.21% to 1.56%) in the control group and 0.30% (95% CI 0.22% to 0.38%) in the group treated antenatally.
- Group 2, involving 11,400 women, included the results of the three studies (none of them randomised) using a regimen of 1500 IU at 28 weeks. These studies included both primigravidae and multigravidae. The rate of postnatal anti-D sensitisation was 1.60% (95% CI 0.37% to 2.83%) in the control group and 0.34% (95% CI 0.28% to 0.40%) in the antenatal treatment group.
- Group 3, involving 4700 women, included the results of the two community-based UK studies which used a regimen of 500 IU at 28 weeks and 34 weeks and which reported results for primigravidae. The rate of postnatal anti-D sensitisation was 0.95% (95% CI 0.18% to 1.71%) in the control group and 0.35% (95% CI 0.29% to 0.40%) in the antenatal treatment group.

The Committee found the data pertaining to Group 3 to be the most informative when considering the clinical and cost effectiveness of RAADP.

4.1.2 Of failures in sensitisation, 30% to 40% appear to be due to treatment failure. The rest appear to be attributable either to logistic failures (women attending for treatment too late, or not at all) or to having been sensitised in a previous pregnancy.

4.1.3 Two doses of anti-D immunoglobulin 500 IU at 28 and 34 weeks into pregnancy appear to be as effective as one 1500 IU dose at 28 weeks.

4.1.4 The Assessment Group used the figures from the meta-analysis reported in Section 4.1.1 (point 3) to build a model to assess the impact of RAADP on HDN-associated deaths in England and Wales. This model suggested that the number of deaths caused by HDN would fall from about 27 per year using current practice to about 15 per year if RAADP were to be given to RhD-negative primigravidae and to about 10 per year if it were given to all pregnant RhD-negative women.

4.1.5. The Committee was also made aware of the other burdens such as fetal loss (including parental grief), the traumas of intra-uterine and postnatal treatment for haemolytic disease, and the costs of caring for children with HDN-induced brain damage.

4.2 Cost effectiveness

4.2.1 Eight studies were found in the literature, of which four used UK costs, but only one described a detailed modelling study applicable to the NHS. The Assessment Group also undertook a modelling procedure (see Section 4.1.4).

4.2.2 The cost effectiveness of RAADP for RhD-negative women having their first child has been considered separately from its cost effectiveness for all pregnant RhD-negative women. This approach has been taken because the more children a woman already has, the less likely she is to have a further pregnancy and the less cost effective RAADP will be.

4.2.3 The following Table, taken from the modelling exercise carried out in the Assessment Report, gives the cost per unit of outcome for several outcome measures. Note that the figures refer to the incremental cost of providing prophylaxis in addition to postpartum prophylaxis.

Table 1. Incremental cost effectiveness of providing RAADP for RhD-negative primigravidae and for all RhD-negative pregnant women.

Cost (£)	Primigravidae vs postpartum anti-D	All RhD-negative vs primigravidae only
Per sensitisation avoided	16,000	17,000
Per case of haemolytic disease avoided	14,000	46,000
Per fetal/neonatal loss avoided	210,000	680,000
Per QALY, for avoidance of disability only (fetal/neonatal loss not included)	12,000	49,000
Per QALY, for avoidance of disability and fetal/neonatal loss taken together (Assuming fetal/neonatal loss is associated with 10 QALYs: see Section 4.3.3)	7,600	28,000

Costs are average of BPL and Baxter dosage regimens at NHS list prices. At discounted prices, costs per unit of outcome will be lower than indicated in the above table.

The model suggests that the cost per sensitisation does not differ significantly between first and later pregnancies. The cost per case of disease avoided and the cost per fetal/neonatal loss avoided are lower for

primigravidae because the number of further children a woman will have is higher for women who have had one child than for women who have had two or more children.

- 4.2.4 Although the Assessment Report showed that it is possible to quantify a cost per life-year gained from each fetal/neonatal loss averted by RAADP, the Committee was unsure that this was an appropriate way to reflect the social value of this intervention. However, the Committee judged that, taken together, the benefits of avoiding the burden of early fetal/neonatal loss (including parental grief, the costs of caring for children who have severe brain damage caused by HDN, as well as the loss of life years of newborn or stillborn infants) make RAADP a cost-effective procedure when there is a moderate or high probability that an RhD-negative woman will have a further child or children. These figures do not allow for the costs avoided of caring for children who would have had severe brain damage caused by HDN.

4.3 Consideration

- 4.3.1 In the process of reaching a conclusion, the Committee considered a number of factors, including the benefits of RAADP in averting fetal/neonatal loss, averting long- and short-term disability to the unborn child and the possibility of long-term damage to mother and/or child of anti-D immunoglobulin. In addition the rights of the mother to make her own informed decision were considered paramount and in this case the Committee also took into account the notion that provision of RAADP would enhance the ability of women to make choices regarding future pregnancies from a position of lower likelihood of anti- RhD sensitisation.
- 4.3.2 The Committee considered that, from examining the benefits from averting major disabilities in subsequent children, RAADP was cost-effective for women having their first child, as most of these women would have a second or subsequent child. For women having a second or subsequent child, however, the cost effectiveness of RAADP would be related to the likelihood of the woman having a further child or children. For this group of women, the benefit from averting potential severe disability in an affected child alone was not considered sufficient to make RAADP cost-effective. However, RAADP becomes more cost effective if the benefit of averting the high physical, emotional and monetary costs placed on parents and other informal (non-paid) carers of disabled children is also taken into account.

4.3.3 The Committee also considered the important issue of averting fetal/neonatal loss and the nature of the effect this would have on both quality of life of the mother and the cost effectiveness of RAADP. It was difficult to ascribe a precise utility value to this aspect of the use of the technology but it could be argued that the loss of a fetus late in pregnancy was equivalent to losing a full lifetime. Whether or not a full lifetime is considered to be lost in these circumstances, the Committee concluded that the loss of a fetus late in pregnancy or at birth was equivalent to a loss of at least 10 quality-adjusted life years (QALYs).

4.3.4 The Committee discussed in detail the possibility that there are circumstances in which RAADP may not be clinically necessary or cost effective. These include when:

- the woman has opted to be sterilised after birth
- the father is RhD-negative, where this is known
- the woman is most unlikely to have another child.

However, it may be difficult for the woman to be certain about these factors. The Committee agreed, therefore, that they should not preclude consideration of RAADP in an individual case. In addition these issues should be discussed between the clinician responsible for prenatal care and the pregnant woman and they should also form part of the general information regarding the relative risks and benefits of RAADP that should be provided as recommended in Section 1.4.

4.3.5 It has been speculated that exposure to anti-D immunoglobulin in utero may affect a baby's immune system, and may also give rise to problems for RhD-negative girl babies later in life when they in turn reproduce. Currently, these are theoretical concerns as there is no evidence of adverse events, even though many babies exposed to AADP have reached adulthood.

4.3.6 The Committee considered the risk of infection with a known pathogen – prion or virus – to be extremely low. The probability that an unknown pathogen with serious adverse outcomes may be present in anti-D immunoglobulin may only be estimated subjectively, and therefore lacks precision. The Committee considered evidence that suggested a subjective risk of contamination of a batch of anti-D immunoglobulin product infected by an unknown agent to be less than 1 in a million. In any case, when an RhD-negative woman gives birth to an RhD-positive child (60% of

births to RhD-negative women), she will also receive anti-D routinely after birth. Under these circumstances, it is estimated that risk of transmission of an unknown pathogen is small and of the order of about three women infected in the UK every 100 years from RAADP, compared with two every 100 years from routine postnatal anti-D administration.

4.3.7 A woman's decision not to be given RAADP should always be respected. The following should also be taken into consideration:

- the birth of an RhD-negative child with an RhD-positive father indicates that the father is heterozygous. In this case, there is only a 50% chance that any subsequent child (with the same father) will be RhD-positive.
- an RhD-negative woman with satisfactory knowledge of the advantages and disadvantages of RAADP might conclude that she would prefer to undertake the prophylaxis, if necessary, only after the birth.

4.3.8 The Committee considered the provision of high-quality information, validated and produced nationally, for healthcare professionals and RhD-negative women to be important, to allow women the opportunity to be adequately informed about their treatment and to decide whether RAADP would be worthwhile in their circumstances. The information should cover both RAADP and prophylaxis where a sensitising event has occurred, either before or at birth, and the availability of genotyping of partners.

5

Implications for the NHS

- 5.1 If RAADP were to be given throughout England and Wales to all RhD-negative women at each pregnancy, the drug and administrative costs would be about £6 million per year. Given that about 30% of hospitals already treat RhD-negative women routinely, and that negotiated prices for anti-D may be lower than list prices, it is unlikely that drug and administrative costs would increase by more than £4 million as a result of this guidance. The cost may be even a little lower if some women decline treatment. Informing women of their options and discovering the father's RhD status also have resource costs that are not readily quantifiable.
- 5.2 Most of the additional work involved in treating pregnant RhD-negative women with RAADP will arise from ensuring that the women being treated are sufficiently aware of the options available for them to make an informed choice about treatment.

- 5.3 Whether RAADP is carried out under the control of a midwife, general practitioner or obstetrician, the person who administers the treatment should have a good working knowledge of the benefits and costs of RAADP compared with postpartum administration, and also of the circumstances that would give greater or lesser benefits to the woman involved.
- 5.4 The production and provision of the high-quality information referred to in 4.3.8 will have a cost impact. However, as this information will cover all use of anti-D, the additional cost attributable to the RAADP component will be small.
- 5.5 The finding of anti-D in a pregnant woman's serum may pose difficulties of interpretation when antenatal prophylaxis has been given. The test will not reveal whether the woman has produced the anti-D herself (that is, has become sensitised) or has been given anti-D prophylaxis relatively recently. Providers of antenatal care should communicate to ensure that whenever anti-D is discovered antenatally in the serum, it is correctly interpreted and acted upon.

6

Further research

- 6.1 To help inform cost-effectiveness decisions, a long-term project is recommended to determine the probability of whether women of different age groups who say they are having their last child actually do so.
- 6.2 The Committee endorses studies into the feasibility of mass testing antenatally for fetal blood group by analysis of circulating fetal DNA in maternal plasma. If fetal Rh blood type could be determined before 28 weeks' gestation, antenatal anti-D prophylaxis would be necessary only for pregnancies where the fetus was RhD positive, and knowledge of the father's blood group would no longer be required.

7

Implementation

- 7.1 All clinicians who provide care for pregnant women including midwives, general practitioners and consultant obstetricians and gynaecologists, should review policies and practices regarding the administration of RAADP for RhD-negative women to take account of the guidance set out in Section 1.
- 7.2 Local guidelines or care pathways on routine antenatal care should incorporate the guidance set out in Section 1.
- 7.3 Arrangements should be made to ensure that responsibility is clearly defined for explaining treatment options to RhD-negative women and that clinicians in both community and hospital-based antenatal clinics are competent in explaining treatment options to RhD-negative women.

7.4 To measure compliance locally with the guidance set out in Section 1, the following criteria should be used:

- a non-sensitised RhD-negative woman who is pregnant is made aware of treatment-options by the clinician responsible for her prenatal care so that she can make an informed choice about treatment and is offered RAADP
- a woman who has made an informed choice for treatment with RAADP receives this treatment

Technical details on the criteria for this audit are given in Appendix D.

7.5 Implementation of those parts of the guidance requiring national input should be coordinated by the NHS at a national level with advice from professional and consumer organisations in the area of concern.

8

Related guidance

8.1 NICE has commissioned guidelines on Routine Antenatal Care from the Women's and Children's Health Collaborating Centre, which it is expected will be completed in autumn 2003.

9

Review of guidance

9.1 This guidance will be reviewed in the light of new evidence in March 2005.

Andrew Dillon
Chief Executive
May 2002

APPENDIX A

Appraisal Committee members

The Appraisal Committee is a statutory committee whose members sit for 3 years. Two meetings are held per month and the majority of members attend one or the other. Declared interests may also exclude a member from individual technology appraisals. The Committee are supplemented by technology specific experts as indicated in Appendix B.

Professor R. L. Akehurst
Dean, School of Health Related
Research
Sheffield University

**Professor David Barnett
(Chairman)**
Professor of Clinical Pharmacology
University of Leicester

Professor Sir Colin Berry
Professor of Morbid Anatomy
St Bartholomew's and Royal London
School of Medicine

Dr Sheila Bird
MRC Biostatistics Unit,
Cambridge

Professor Martin Buxton
Director of Health Economics Research
Group
Brunel University

Dr Karl Claxton
Lecturer in Economics
University of York

Professor Sarah Cowley
Professor of Community Practice
Development
Kings College, London

Dr Nicky Cullum
Reader in Health Studies
University of York

Mr Chris Evennett
Chief Executive
Mid-Hampshire Primary Care Group

Professor Terry Feest
Clinical Director and Consultant
Nephrologist
Richard Bright Renal Unit, And
Chairman of the UK Renal Registry

Ms Jean Gaffin
Formerly Executive Director
National Council for Hospice and
Specialist Palliative Care Service

Mrs Sue Gallagher
Chief Executive
Merton, Sutton and Wandsworth
Health Authority

Dr Trevor Gibbs
Head, Global Clinical Safety &
Pharmacovigilance

IaxoSmithKline

Mr John Goulston
Director of Finance
The Royal Free Hampstead NHS Trust

Professor Philip Home
Professor of Diabetes Medicine
University of Newcastle

Dr Terry John
General Practitioner
The Firs, London

Dr Diane Ketley
Research into Practice Programme
Leader
NHS Modernisation Agency

Dr Mayur Lakhani
General Practitioner, Highgate Surgery,
Leicester and Lecturer,
University of Leicester

Mr M Mughal
Consultant Surgeon
Chorley and South Ribble NHS Trust

Mr James Partridge
Chief Executive
Changing Faces

Professor Philip Routledge
Professor of Clinical Pharmacology
University of Wales

**Professor Andrew Stevens
(Vice Chairman)**
Professor of Public Health
University of Birmingham

Dr Cathryn Thomas
General Practitioner/Senior Lecturer
Department of Primary Care & General
Practice
University of Birmingham

APPENDIX B

Sources of evidence

The following documentation and opinion was made available to the Committee:

a. Assessment report:

- prepared by the School of Health and Related Research, University of Sheffield (*A Review of the Clinical and Cost Effectiveness of Routine Anti-D Prophylaxis for Pregnant Women who are Rhesus (RhD) Negative*, October 2001)

b. Manufacturer/sponsor submissions:

- Baxter Healthcare Ltd
- Bio Products Laboratory

c. Professional and patient group submissions :

- Association of Radical Midwives
- British Association of Perinatal Medicine
- British Committee for Standards in Haematology
- National Blood Service
- National Childbirth Trust
- Royal College of General Practitioners
- Royal College of Midwives
- Royal College of Obstetricians and Gynaecologists
- Royal College of Physicians, Royal College of Pathologists and British Blood Transfusion Society
- United Kingdom Central Council for Nursing, Midwifery and Health Visiting

d. External expert and patient advocate submissions:

- Cynthia Clarkson, Trustee for Research Networker, National Childbirth Trust
- Sue Maguire, Research Networker, National Childbirth Trust
- Professor S C Robson, Head of Department of Obstetrics & Gynaecology, Royal Victoria Infirmary, Newcastle upon Tyne
- Professor Marcela Contreras, Professor of Transfusion Medicine, NBS and Royal Free University College Hospital Medical School
- Louise Silverton, Deputy General Secretary, Royal College of Midwives

APPENDIX C

Patient information

Guidance on the use of routine antenatal anti-D prophylaxis for RhD-negative women

The patient information in this appendix has been designed to support the production of your own information leaflets. You can download it from our website at www.nice.org.uk where it is available in English and Welsh. If you would like printed copies of the leaflets please ring the NHS Response Line on 0870 1555 455 and quote reference no N0093 for the English patient leaflet and N0094 for the bi-lingual patient leaflet.

What is NICE guidance?

The National Institute for Clinical Excellence (NICE) is a part of the NHS. It produces guidance for both the NHS and patients on medicines, medical equipment, diagnostic tests and clinical and surgical procedures and where they should be used.

When the Institute evaluates these things, it is called an appraisal. Each appraisal takes around 12 months to complete and involves the manufacturers of the drug or device, the professional organisations, and the groups who represent the people that the guidance concerns.

NICE was asked to look at the available evidence on routine antenatal anti-D prophylaxis and provide guidance that would help the NHS in England and Wales decide where it should be used in rhesus (RhD)-negative women.

What does RhD negative mean?

The rhesus factor is found in the red blood cells. People who are rhesus positive have a substance known as D antigen on the surface of their red blood cells – they are said to be RhD positive. People who are rhesus negative do not have the D antigen on their blood cells – they are RhD negative. Whether a person is RhD positive or RhD negative is determined by their genes – that is, it is inherited from a parent.

Why does RhD status matter?

RhD status matters if a woman who is RhD negative becomes pregnant with a baby who is RhD positive. This can only happen if the baby's father is RhD positive – but not all children who have an RhD-positive father will be RhD-positive, because the father may have both RhD-positive and RhD-negative genes.

If any of the blood cells from an RhD-positive baby get into the blood of an RhD-negative woman, she will react to the D antigen in the baby's blood as though it is a foreign substance and will produce antibodies. This is not usually dangerous in a first pregnancy, but in later pregnancies the antibodies in the mother's blood can cross the placenta and attack the blood cells of an RhD-positive unborn baby. This can cause 'haemolytic disease of the newborn', which is also known as HDN. HDN can be very mild

and only detectable by laboratory tests. But it can be more serious and cause the baby to be stillborn, severely disabled or to die after birth as a result of anaemia (lack of iron in the blood) and jaundice.

Each year in England and Wales there are about 62,000 births of RhD-positive babies to RhD-negative women.

In England and Wales, about 500 babies develop HDN each year, and must be closely monitored. Each year about 25–30 babies die from HDN. About 15 children each year will have major permanent developmental problems as a result of HDN, and a further 30 will have minor developmental problems.

The most common time for a baby's blood cells to get into the mother's blood is at the time of birth. But it can happen at other times, for example during a miscarriage or abortion, or if something happens during the pregnancy such as having an amniocentesis, chorionic villus sampling, vaginal bleeding or external cephalic version (turning the baby head down). An event that could cause the mother to produce antibodies against the D antigen is called a 'potentially sensitising event'.

What is anti-D prophylaxis?

Prophylaxis is the word given to a medicine that is used to prevent something happening. Anti-D prophylaxis means giving anti-D immunoglobulin to prevent a woman producing antibodies against RhD-positive blood cells and so to prevent the development of HDN in an unborn baby. Anti-D immunoglobulin is made from a part of the blood called plasma that is collected from donors. The production of anti-D immunoglobulin is very strictly controlled to ensure that the chance of a known virus being passed from the donor to the person receiving the anti-D immunoglobulin is very low – it has been estimated to be 1 in 10,000 billion doses.

Routine antenatal anti-D prophylaxis (RAADP) is given by injection to pregnant women who are RhD-negative usually at weeks 28 and 34 of their pregnancy. After the birth, a blood sample will be taken to test the baby's blood group. If the baby is RhD positive, a mother who is RhD negative will be given a further injection of anti-D immunoglobulin – this is known as postnatal anti-D prophylaxis and is not the subject of this NICE guidance. If an RhD-negative woman has a potentially sensitising event during the pregnancy she will be offered anti-D prophylaxis at the time of the event: this is known as antenatal anti-D prophylaxis or AADP.

Occasionally anti-D prophylaxis causes allergic responses in the mother, but these are rare.

What has NICE recommended about the use of anti-D prophylaxis?

This NICE guidance covers only RAADP (that is anti-D prophylaxis given routinely usually at weeks 28 and 34 of pregnancy). It does not cover AADP or postnatal anti-D prophylaxis – both of these types of anti-D prophylaxis are covered by the Royal College of Obstetricians and Gynaecologists' 'Green Top' 1999 guideline: Use of Anti-D Immunoglobulin for Rh Prophylaxis.

NICE has made the following recommendations about RAADP.

If you are pregnant and are RhD negative you should be offered RAADP if you have not already been 'sensitised', this means that you have already have antibodies to the D antigen in your blood that can be detected by a blood test at the beginning of your pregnancy.

If you are pregnant and are RhD-negative, your midwife, obstetrician or GP (that is whoever is responsible for your antenatal care) should discuss RAADP with you and explain the options available so that you can make an informed choice about treatment. The difference between RAADP and AADP should be clearly explained to you.

The healthcare professional should discuss the situations where anti-D prophylaxis would be neither necessary nor cost effective. Such situations might include those where a woman:

- has opted to be sterilised after the birth of the baby
- is in a stable relationship with the father of the child, and it is certain that the father is RhD negative
- is certain that she will not have another child after the current pregnancy.

You should be offered RAADP even if you have already had AADP for a potentially sensitising event earlier in your pregnancy. You should be offered postnatal anti-D prophylaxis whether or not you have had AADP or RAADP.

NICE recommends that high-quality information, which has been produced and checked at a national level, should be available to RhD-negative women and the relevant healthcare professionals.

What should I do?

If you are pregnant and RhD-negative then you can discuss this advice with the midwife, obstetrician or GP at your next appointment.

Will NICE review its guidance?

Yes. The guidance will be reviewed in March 2005.

Further information

Further information on NICE, and the full guidance issued to the NHS is available on the NICE website (www.nice.org.uk).

The guidance can also be requested from 0870 555 455, quoting reference N0091.

If you have access to the Internet and would like to find out more about anti-D prophylaxis visit the NHS Direct website: www.nhsdirect.nhs.uk If you would like to speak to NHS direct please call them on 0845 46 47.

APPENDIX D

Technical detail on the criteria for audit of the offering of routine anti-D prophylaxis for RhD-negative women

Possible objectives for an audit

An audit on the appropriateness of managing the care of RhD-negative women could be carried out to ensure that these women are informed of their treatment options, that RAADP is offered to all non-sensitised RhD-negative pregnant women, and that it is prescribed for those women who choose treatment. The woman's choice should also be recorded.

Women to be included in an audit and time period for selection

All RhD-negative women seen in antenatal clinics over a sensible period of time for audit data collection, for example, 3 months. To carry out the audit using the measures provided, the sensitised status of women will need to be recorded. To apply the audit measures, RhD-negative women who are unsensitised will need to be identified.

Measures to be used as a basis for an audit

The following measures can be used in a local audit of the appropriateness of managing the care of RhD-negative women:

Criterion	Standard	Exception	Definition of terms
1. A pregnant woman who is RhD-negative and is unsensitised is informed of treatment options and is offered RAADP	100% of unsensitised RhD-negative pregnant women	None	Clinicians should agree locally on how the giving of information about treatment options is to be documented for audit purposes
2. RAADP is prescribed for an RhD-negative unsensitised woman who has chosen treatment			Clinicians should agree locally on how a woman's decision to decline treatment is to be documented for audit purposes

Clinicians should review the findings of measurement, identify if practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that desired improvement is being achieved.

